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Poh K. Hui

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WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER

KISHORE, GOLLAMUDI S

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The amendment dated 4-3-09 is acknowledged.

Claims included in the prosecution are 87-117.

In view of applicant's arguments, Unger (6,521,211) is removed from the rejections.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 87-111 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13°-25° C, and drying the precipitate (see example 1, 2, 6, and claim 1). The concentration of sphingomyelins in the solvent is 2-20 mg/ml (column 6, lines 44-48). Nyberg et al.

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specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Nyberg et al and Unger teach steps a, b and c. What is lacking in Nyberg is the teaching of the preparation of lipid suspensions or liposomes using the lipids of Nyberg et al and Unger (steps d and e).

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

It would have been obvious to one of ordinary skill in the art, if lipid encapsulation of an active agent is desired, to use the steps taught by Kissel or Papahadjopoulos or

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Lenk to prepare liposomes since it is an art known method of preparing liposomes.

Although the references do not teach all of the non-aqueous solvents such as propylene glycol and their amounts, since the principle of precipitation is the same and since Nyberg teaches the use of suitable solvent systems (col. 3, lines 6-1 and col. 9, lines 54-57), in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any solvent which is suitable with a reasonable expectation of success. Similarly, since the purpose is to dissolve the lipids in a solvent, it would have been obvious to one of ordinary skill in the art to use suitable temperatures to achieve the complete dissolution of the phospholipids. Applicant's claim limitation of sterilizing filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant argues that the claimed process included contacting at least two individual lipids with a first non-aqueous solvent that causes the lipids to dissolve and that Nyberg does not teach a process of making a lipid blend from individual lipids which is an important element of the claimed invention. According to applicant, Nyberg teaches beginning with a mixture and separating out phospholipids for further use and not preparing a lipid blend from individual lipids. This argument is not persuasive. In Nyberg, the starting mixture contains three individual phospholipids and after the step of contacting the lipid solution with the second non-aqueous solvent which causes the

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lipids to precipitate, the sphingomyelin fraction still contains other phospholipids in small amounts (see Example 1 on columns 7 and 8 of Nyberg and Example 4). Furthermore, col. 6, lines 15-20 of Nyberg shows that after precipitation of the sphingomyelin fraction, one can precipitate the remaining phospholipids (phosphatidylcholine and phosphatidylethanolamine) can be precipitated together at 0 to 5 degrees using the solvent mixture. Instant claims do not recite any specific amounts of individual phospholipids and therefore, the reference still meets the requirements of instant steps a to c. The examiner also points out that Nyberg also teaches the knowledge in the art of the use of phospholipids in the preparation of liposomes (col. 1, lines 18-30).

Applicant's arguments that Kissel, Papahadjopoulos, Kikuchi and Lenk do not teach the missing elements of the claims as amended and that these references do not teach lipid blend prior to liposome preparation are not persuasive since these references clearly teach that either single phospholipids or mixtures of phospholipids are routinely used in the preparation of liposomes. These references show the use of pure phospholipids in the preparation of liposomes and applicant has not shown any unexpected results resulting from the use of an additional precipitation step by direct comparison using the pure phospholipids taught by Kissel, Papahadjopoulos, Kikuchi and Lenk.

3. Claims 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Nyberg, Unger, Kissel, Kikuchi, Papahadjopoulos and Lenk have been discussed above. These references do not teach how to prepare liposomes containing ultrasound contrast agents containing perfluoropropane, that is, exchange air with perfluorohydrocarbons in a vacuum chamber.

Swaerd-Nordmo while disclosing vesicular preparations containing contrast agents teaches that the contrast agents can be incorporated by the exchanging perfluoropropane in a vacuum chamber (col. 3, Example 1). Various phospholipids which could be used are taught on col. 3, line 60 through col. 4, line 28).

It would have been obvious to one of ordinary skill in the art to use the method of Swaerd-Nordmo to encapsulate perfluoropropane in the teachings of the primary references if the intended purpose is to use the liposomes for the delivery of ultrasound contrast agents since such a method is known in the art as taught by Swaerd-Nordmo.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos, Kikuchi and Lenk. Applicant argues that Swaerd-Nordmo fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of encapsulating ultrasound contrast agents; Nyberg teaches the preparation of phospholipids using instant steps a to c.

4. Claim 115-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, in view of Swaerd-Nordmo, further in view of Unger (6,071,495).

The teachings of Nyberg, Unger, Kissel, Papahadjopoulos, Lenk, Kikuchi and Swaerd-Nordmo have been discussed above. What is lacking in these references is the final sterilization of the product. Such a sterilization however, would have been obvious to one of ordinary skill in the art if the preparation is used for human administration especially by an injection mode since sterilization of contrast agent containing liposomes by gamma-ray irradiation is known in the art as taught by Unger 6,071,495) (see col. 17, line 42 through col. 18, line 14).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos, Kikuchi and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of sterilization; Nyberg teaches the preparation of phospholipids using instant steps a to c.

5. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Unger 6,416,740.

The teachings of Nyberg, Kissel, Papahadjopoulos and Lenk have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Nyberg, Kissel, Papahadjopoulos and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of art known use of the claimed combination of the phospholipids; Nyberg teaches the preparation of phospholipids using instant steps a to c.

6. Claims 87-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

In essence, these references teach steps d and e of claim 87. Instant steps a-c in claim 87 just recite re-precipitation of the lipids used in the formation of lipid suspension. The criticality of these steps is unclear to the examiner if one is using pure phospholipids just as used in Kissel, Papahadjopoulos, Lenk and Kikuchi. Since the removal of impurities by precipitation is well-known in the art of chemistry, instant claims are deemed obvious to one of ordinary skill in the art. The reference of Nyberg which teaches selective precipitation of sphingomyelins is already of record. Applicant's claim limitation of sterilizing filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the references do not teach the preparation of lipid blend as claimed. The examiner points out that the use of pure phospholipids and their mixtures

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for the preparation of liposomes is clearly evident from the references and applicant has not shown that the step of precipitating the phospholipids and then re-dissolving them in a solvent prior to the addition of the aqueous medium for the preparation of liposomes is critical by direct comparison with the prior art preparation of liposomes using pure phospholipid mixtures.

7. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger 6,416,740.

The teachings of Kissel, Papahadjopoulos, Lenk and Kikuchi have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Kissel, Kikuchi, Papahadjopoulos and Lenk. Applicant argues that Unger fails to teach or suggest methods to make a lipid blend as claimed. The examiner points out that this reference is combined for its teachings of art known use of the claimed combination of the phospholipids.

8. Claims 87-111 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or

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Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Munechika discloses a method of preparation of liposomes. The method involves dissolving the lipids in an organic solvent, precipitating the lipids using a second organic solvent and hydrating the precipitate with an aqueous solution to form liposomes (col. 2, line 8 through col. 3, line 61 and examples). Munechika differs from instant method in that the precipitate is directly added to the hydrating medium instead of dissolving again in an organic solvent and adding the hydrating aqueous solution.

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent

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taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

It would have been obvious to one of ordinary skill in the art to dissolve the precipitate containing the lipids in an organic medium again and adding the aqueous medium to this solution with a reasonable expectation of success since the references of Kissel, Papahadjopoulos, Lenk and Kikuchi all show that this method is a routinely practiced method in the preparation of liposomes.

9. Claims 112-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi and Lenk have been discussed above. These references do not teach how to prepare liposomes containing ultrasound contrast agents containing perfluoropropane, that is, exchange air with perfluorohydrocarbons in a vacuum chamber.

Swaerd-Nordmo while disclosing vesicular preparations containing contrast agents teaches that the contrast agents can be incorporated by the exchanging perfluoropropane in a vacuum chamber (col. 3, Example 1). Various phospholipids which could be used are taught on col. 3, line 60 through col. 4, line 28).

It would have been obvious to one of ordinary skill in the art to use the method of Swaerd-Nordmo to encapsulate perfluoropropane in the teachings of the primary

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references if the intended purpose is to use the liposomes for the delivery of ultrasound contrast agents since such a method is known in the art as taught by Swaerd-Nordmo.

10. Claims 115-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination in view of Swaerd-Nordmo (6,165,442) as set forth above, further in view of Unger (6,071,495).

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi, Lenk and Swaerd-Nordmo have been discussed above. What is lacking in these references is the final sterilization of the product. Such a sterilization however, would have been obvious to one of ordinary skill in the art if the preparation is used for human administration especially by an injection mode since sterilization of contrast agent containing liposomes by gamma-ray irradiation is known in the art as taught by Unger (6,071,495) (see col. 17, line 42 through col. 18, line 14).

11. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Munechika (5,662,931) in combination with Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger 6,416,740.

The teachings of Munechika, Kissel, Papahadjopoulos, Kikuchi and Lenk have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

The reference of Shinitzhy (4,474,773) which shows that instant method of precipitation is routinely practiced in the fractionation of phospholipids is cited of interest (col. 4, lines 30-47).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore whose telephone number is (571)

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272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK